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REVIEW ARTICLE

What is the future of Bee-Pollen?

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Summary

In the last two decades many papers have been published on issues concerning bee pollen. Some have related to nutritional and therapeutic claims supported by scientific based evidence and many have dealt with quality control questions and validation of the methodologies that allow bee pollen producers to have sufficient knowledge to provide the market with high quality products. The quality of the product starts to be influenced by the bees at pollen collection, and includes harvest by beekeepers and technologies used during storage. This review summarises information available at each of these stages. In the near future research needs to develop legislation in order to have Harmonised Standard Quality Control. It is clear that there is quite a long road until bee pollen will be able to take a place in modern phytomedicine. The main difficulty for the use of bee pollen in therapy lies in the wide variation of its composition, and thus of its biological activity, depending on its botanical origin. In the first place beekeepers should offer a good selection of different specific bee pollen. Indeed, the harvest of monofloral pollen is possible, but for the time being it is a relatively rare specialty. Another possibility of having more standardized bee pollen is to mix different pollen types to obtain a constant composition, and thus also consistent biological activity. For this purpose biological parameters like antioxidant activity and vitamin content should be included in a future bee pollen standard. Monofloral or standardized bee pollen should be tested in future biological and clinical studies. The biological and pharmacological properties of the monofloral pollen types should be determined and the biologically active substances identified. Then pollen types with optimal pharmacological properties can be evaluated for human therapy.

Keywords: bee pollen, nutritional effects, biological activity, pharmacological activity, therapeutical application

Introduction

Once bee pollen was defined in legislation as food, the nutritional value of this product became important. It contains high concentrations of reducing sugars, essential amino acids and unsaturated/saturated fatty acids, minerals as Zn, Cu, Fe, and high K/Na ratio and significant quantities of several vitamins: provitamin A, vitamin E (tocopherol), niacin, thiamine, folic acid and biotin. The amount of these nutrition-relevant components is largely dependent on the botanical source of the pollen.

The nutritional content of bee pollen may be partly released by digestive juices, however only a proportion of bee pollen constituents is assimilated by humans. Bee pollen is a product with added value because it can also be used for certain health benefits such as an antioxidant, and an anti-inflammatory, and / or an antimicrobial agent. Research evidence includes experiments with cell lines, animals and humans. The main biologically active compounds are the flavonoids and the phytosterols. The most outstanding therapeutic action of clinical value is its anti-prostatitic effect. However this effect has been most effectively shown with pollen preparations of flower pollen (collected directly from flowers by humans means), although there are also positive results with bee pollen. Pollen based vaccines were successfully used in double blind clinical trials for desensitization against hay fever and therefore merit further investigation (Khinchi *et al.*, 2002; Moingeon *et al.*, 2008). Besides, there are significant claims of antianaemia, anti-atherosclerotic, anti-osteoporosis and anti-allergic effects, but mostly in animal studies. Human pre-clinical trials are scarce and sometimes absent.

Bee pollen is the result of the agglutination of flower pollens, made by worker honey bees, with nectar (and/or honey) and salivary substances, and collected at the hive entrance (Campos *et al.*, 2008). It is recovered by humans at the entrance of the hive and is therefore a wild product, produced without manipulation.

For centuries the nutritional value was surrounded by mystery. The consumption of plant producing seed, (or the pollen), is praised in the Bible, Genesis 1:29:

"*and God said, See, I have given you every plant producing seed, on the face of all the earth, and every tree which has fruit producing seed: they will be for your food".*

The ancient Egyptians describe it as "a life-giving dust". In ancient Greece the pollen pellets, carried on the bee's legs were considered to be made of wax. Aristotle in his *Historia animalium* observes that they resemble wax in hardness but are in reality sandarace or bee-bread. Some of the "Fathers of Western Medicine" (Hippocrates, Pliny the Elder, and Pythagoras) trusted the healing qualities of bee pollen; they often prescribed it to their patients. The name bee-bread persisted for many centuries. Pollen (a Latin word for fine flour or dust) was used for the first time by John Ray in *Historia plantarum* (1686). Bee collected pollen began to be used for human nutrition on a larger scale only after the Second World War, when pollen traps were developed and became readily available.

Bee pollen is defined as food, but due to the small quantities that are generally consumed, it should be rather regarded as a functional food or a food additive. At present there is no international pollen standard defining compositional requirements, although some countries have national standards. Work carried out by the "Bee-pollen group" of the International Honey Commission (IHC) in order to establish an International Bee-pollen Standard, culminated in a review of the composition of bee-pollen and a proposal for a standard (Campos *et al.,* 2008). Ideally, it should include not only physico-chemical and microbiologic quality criteria, but also requirements for relevant biologically activities. In this review we attempt to summarise the knowledge on this valuable bee product in regard to nutrition and possible health enhancing and therapeutic applications for a future possible market. A separate section on bee pollen collection and harvest is included, as knowledge on this subject has a decisive effect on the quality and the nutritional and therapeutic properties of bee pollen. Also, it should be borne in mind that flower pollen is produced in much larger quantities than bee pollen, as it can be easily harvested by machines, e.g. maize or *Gramineae* pollen. Thus, extensive health relevant research has been conducted on pollen preparations from non bee pollen, here called flower pollen. Indeed, the main applications in modern medicine have been derived from such pollen. This pollen is offered in the form of specific products, marketed under different names. Cernitron, Cernitol and Prostat/ Poltit are grass or rye pollen preparations while Cernitin and Graminex contain different flower pollens. Here we cover research carried out on both pollen types (bee pollen and flower pollen harvested by humans) where similar biological activity has been reported for both.

Pollen harvest

Which pollen types are gathered by the bees?

The pollen types contained in the bee pollen loads carried into the hives by bees can be easily analysed by microscopic analysis, however this method can usually only determine mostly plant family or genera, rather than species. Another approach, by which the exact plant type can be determined, is the analysis of pollen flavonoid and phenolic profile (Campos *et al.,* 1997; Campos *et al.,* 1998). The first approach is generally carried out routinely in pollen and bee pollen quality control.

The present knowledge on the types of bee pollen gathered by bees has been recently reviewed (Keller *et al.,* 2005 a & b). In Switzerland 5 main pollen types as *Zea mays*, *Trifolium repens, Taraxacum* officinallis, *Plantago sp*. and *Brassica napus,* yield 60% of the total gathered pollen. The situation is similar in Italy and Scotland where studies on the botanical composition of bee pollen were conducted (Keller, 2005a). The different studies show that bees are very selective when gathering bee pollen and that the bulk of the pollen generally comes from a few plant species. Other countries like Portugal (Campos *et al.,* 1994b), Turkey (Bilisik *et al*., 2008) and Spain (Serra Bonvehi & Escola Jorda, 1997) confirm similar data. Knowledge of the origin of the flower species is very important, because as demonstrated later in this review, biological activity is directly related to composition.

Pollen harvest, purification and storage

For optimal bee pollen quality the technology of pollen harvesting, purification and storage is a important issue. Beekeepers collect this product by means of bee pollen traps; Keller *et al.* (2005 a & b) deal extensively with this collection practice. There is a large variety of different trap designs, but all consist of some type of grid which removes the bee pollen pellets from some of the returning foragers as they enter the hive. The percentage of bee pollen actually retained in a trap may be quite variable, but will always be considerably less than 100%. The efficiency of a trap at one colony could vary between 3 and 25% during the course of the vegetative period. Assuming an average trap efficacy of 20% the amount gathered by the bee pollen trap varies from 1.1 to 40.4 kg per colony. In Europe, this varied mostly between 1.4 and 9.2 kg. This difference is probably the result of a longer vegetative period, during which pollen was collected. At most locations, the amount harvested in honey bee colonies is subject to considerable fluctuations during the course of the year. In apiaries specialized on the production of bee pollen in countries with a longer vegetative period up to 10 to 20 kg per colony can be harvested, the normal however is lower, about 5-15 kg per hive.

A part of the pollen collected by bees is transformed to bee bread inside the hive and is a rare speciality, that is sold in health food stores, because the collection from the hive is very labour intensive. For that purpose, at times of intensive pollen foraging, newly built combs are placed between the hive entrance and the brood combs, with a queen separator grid to split them from the brood combs. This is the place which will be preferentially filled with bee pollen. This product is mixed with honey and bee secretions and stored in the combs. Bee bread undergoes lactic acid fermentation and can be thus preserved. When the combs are full, the bee bread is harvested by means of a scraper and filled into a jar, where it is mixed with honey. This can also be harvested or sold in the combs, however it is very rare.

Fresh bee collected pollen contains about 20-30 g water per 100 g. This high humidity is an ideal culture medium for micro-organisms such as bacteria and yeast. For prevention of spoilage and for preservation of a maximum quality bee pollen has to be harvested daily and immediately placed in a freezer. After two days of storage in the freezer, any pest insects will be killed (Moosbeckhofer & Ulz, 1996). After thawing bee-pollen can be kept only for a few hours and should be further processed as soon as possible.

Fresh, purified bee-pollen can be frozen and stored under nitrogen until consumption for preservation of optimal biological and nutritive properties, keeping the maximum enzymatic activity, essential for beneficial nutritional effects on the intestine (Percie du Sert, 1998 and 2002; Wang *et al.,* 2007). Indeed, storage of normal dried bee pollen for one year at room temperature will reduce the free radical scavenging capacity of bee pollen by 50% (Campos *et al.,* 2003). The easiest procedure is to pack the product in vacuum and place into air-tight containers or plastic bags for food purposes. Bee pollen is best dried in an electric oven, where humidity can continuously run off. The maximum temperature is 40°C and the drying time should be as short as possible in order to avoid losses of volatile compounds (Collin *et al.,* 1995). Recent research shows that vitamins are lost after drying bee pollen both at 42°C and 32°C: the content of the vitamins C, E, A decreased by an average of 31% under both drying conditions (Szcesna *et al.,* 1995; Oliveira, 2006). As most of the marketed bee pollen today is produced by oven drying, this technology has to be improved e.g. by freeze-drying. The collected pollen pellets can contain impurities which should be removed, most efficiently by air with specially constructed purifiers. The air should be free of dust and bacteria. Pure bee pollen should be stored in a cool, dry place, in well closed glass or plastic recipients.

Pollen in nutrition

Nutritionally relevant components

Recently the composition of pollen has been reviewed (Campos *et al.*, 2008). What is immediately apparent is the large variation between the minimum and maximum values. This is probably due to the variation of the pollen origin floral sources analysed, as it is known that the pollen composition of the different species vary greatly depending on their botanical type (Stanley and Linskens, 1974; Campos 1997). Some variation can also be due to the different quantification methods that have been used in the different publications. The composition has been compared with nutritional requirements for the different components but it has been assumed that when a heaped tablespoon of bee pollen is fully ingested this correspond to 15 g of bee pollen. The data in table 1 shows that contribution of the main nutritional components is in most cases relatively small. Probably depending on the pollen botanical source, the contribution of dietary fibre and protein can be significant and reach 20% of the required daily intake (RDI) values. It was claimed that 15g of the examined Spanish bee pollen was enough to cover the body requirements for free amino acids (Peris, 1984; Nagai *et al.,* 2007). However, this is true only for certain types of pollen, particularly rich in amino acids (Table 1). Only about 3% of the total lipids are free fatty acid, about half of them are the unsaturated acids oleic, linoleic (omega-6) and linolenic (omega-3) (Stanley and Linskens, 1974). Other physiologically important compounds are the sterols. There is a significant nutritional contribution from most of the vitamines present in pollen: provitamine A, vitamine E (tocopherol), niaccin, thiamine, folic acids and biotin. Specially in those cases, where high values have been measured, while in some pollen types the content is lower. Regarding minerals, bee-pollen is a good source of all the elements for which there is a RDI, excepting phosphorus and calcium. Here again, the variation of the compositional values results in the difference of the RDI coverage.

The contribution of the bee to bee pollen composition from nutritional point of view is relatively small and it concerns mainly the soluble carbohydrates (Solberg & Remedios, 1980) (mainly glucose and frutose) and they are not so important from nutritional point of view. Bee pollen contains also relatively high amounts of polyphenols and the flavonoids are the main compounds, most of them occur in pollen as glycosides (Stanley and Linskens, 1974; Markham & Campos, 1996). In one study it varied between 1293 and 8243 mg/100 g, in another, between 530 and 3258 mg/100 g (Campos *et al.,* 2003; Leja *et al.*, 2007).

Pollen digestion

Doubts have been raised, whether the tough shell of pollen can be breached and digested by humans. It was discovered in animal experiments that pollen did not retain its content after leaving the

Table 1. Pollen Composition and Nutritional Requirements

Composition according to (Campos *et al.,* (2008)* - RDI (Required Daily Intake) requirements according to (Deutsche Gesellschaft für Ernährung, 2000), average RDI values have been assumed.

Main Components	**g in 100 g**	**% RDI for 15 g Pollen**	**RDI* (g/day)**
Carbohydrates (fructose, glucose, sucrose, fibers)	13-55	1 – 4.6	320
Crude fibers	0.3 – 20	0.3 – 18	30
Protein	10 – 40	5.4 – 22	50
Fat	1 – 13	0.1 – 4	80
Vitamines	**mg in 100g**	**% RDI for 15 g Pollen**	**RDI (mg/day)**
Ascorbic acid (C)	7 – 56	2 – 15	100
b-Carotin (provitamine A)	1 – 20	30 – 600	0.9
Tocopherol (vitamine E)	4 – 32	8– 66	13
Niacin (B3)	4 – 11	7 – 20	15
Pyridoxin (B6)	0.2 – 0.7	4 – 13	1.4
Thiamin (B1)	0.6 – 1.3	15 – 32	1.1
Riboflavin (B2)	0.6 – 2	12 – 42	1.3
Pantothenic acid	0.5 – 2	2 – 9	6
Folic acid	0.3 – 1	20 – 67	0.4
Biotin (H)	0.05 – 0.07	30 – 42	0.045
Minerals			
Potassium (K)	400 – 2000	5 – 27	2000
Phosphor (P)	80 – 600	2 - 16	1000
Calcium (Ca)	20 – 300	0.5 – 7	1100
Magnesium (Mg)	20 – 300	2 – 23	350
Zink (Zn)	3 – 25	10 – 79	8.5
Manganese (Mn)	2 – 11	15 – 85	3.5
Iron (Fe)	1.1 – 17	2 – 37	12.5
Copper (Cu)	0.2 – 1.6	4 – 36	1.2

digestive tract. This gave rise to the hypothesis that the nutritional content of pollen was released by the digestive juices in animals (Schmidt & Schmidt, 1984; Roulston & Cane, 2000). In humans it was once shown that pollen was absorbed in the digestive tract (Jorde & Linskens, 1974) or that it was partly digested, (Franchi *et al.*, 1997) whereas there were differences in the degree of digestion of poppy and hazelnut pollen, with an average degree of digestibility of 15% for carbohydrates and 53% for proteins. In this case it has been hypothesized that pollen was insufficiently digested and that cracking would improve the digestibility and bioavailability (Rimpler, 2003). Different companies offer cracked bee pollen, claiming that this product is better digested. On the other hand, there are many studies in humans with whole bee pollen (see next section) showing that a part of the bee pollen content is digested and is bioavailable. However maceration of pollen for several hours in water or other liquids is recommended in order to improve digestibility, this method is used also for other heavy digestible grain products.

Nutritional effects

Different nutritional effects of bee pollen in mice have been reviewed by Chauvin (1987). Assorted bee pollen types were fed in different proportions (10 to 50%) mixed with the normal food consisting of maize and the controls were provided with a casein supplement. The mice which ingested bee pollen had a faster and better gain of weight and ate less total food than the controls. Probably bee pollen improved the food digestibility. Both aqueous extracts and whole bee pollen were fed and had similar effects. Aqueous bee pollen was prepared by letting the pollen swell for several hours in cold water. This product acts positively mostly on the female rats, while it causes a slowing down of the growth of the male rats. Bee pollen nutrition also caused an increase of reproduction by 40 to 80% in comparison to the controls. This increase induced simultaneously an hyperglycaemic similar to the one caused by the hypophyse hormones (Chauvin, 1968 and 1987).

Mice feed with bee pollen from different plants for 6 months showed an increase in reproduction rates (Slijepcevic *et al.,* 1978). These results are in line with the previous study. In another study the ingestion of bee pollen by rats revealed that it improved the maternal nutrition without affecting the normal foetal development and thus suggested it might be a favourable nutrient during pregnancy (Xie *et al.*, 1994). However the hyperglycaemic effect revealed in the preceding assay can not be underestimated.

It has been shown that chickens fed with bee pollen led to a better development of the small intestine villi from the duodenum, jejunum and ileum. These findings suggest that bee pollen promoted the early development of the digestive system (Wang *et al.*, 2007).

Bee pollen can also be a suitable food for sportsmen. Indeed, competitive sportsmen in some countries have used bee pollen extract as a dietary supplement in the belief that it can lead to an improvement in performance. Controlled experiments indicate that no positive benefit was obtained from the use of this supplementation. However, the number of training days missed due to upper respiratory tract infections was much less in the bee pollen treatment group (4 days) than in the placebo group (27 days). In a study of longer duration, this difference could lead to an improved performance by the bee pollen treatment group due to fewer interruptions in training (Maughan & Evans, 1982).

Potentionally hazardous components

Trace amounts of hepatotoxic pyrrolizidine alkaloids were found in pollen of *Echium vulgare, E. plantagineum, Senecio jacobaea, S. ovatus, and Eupatorium cannabinum* (Boppre *et al.,* 2008). In Middle and Northern Europe these pollens are not among the main pollen grains gathered by bees, however in Southern Europe the two *Echium* plants are more diffused and are gathered by bees in larger amounts (Campos *et al.*, 1994; Serra Bonvehi, 1997).

Pollen should be tested to comply with standards for microbiological purity and residues of contaminants. (The allergy issue cannot be ignored). The different contaminants of bee-pollen have been recently reviewed. (Bogdanov, 2006).

Health claims based on biological and/or therapeutic activities

The main biological components of bee pollen are the phenolic acid derivatives and polyphenolic compounds, mostly flavonoid glycosides. The flavonoids are so called secondary plant compounds which have different important physiological and pharmacological activities. They possess diverse biological properties such as antioxidant, anti-ageing, anti-carcinogen, anti-inflammatory, anti-atherosclerosis, cardioprotective and improved endothelial function. Most of these biological actions have been attributed to their intrinsic reducing capabilities. They may also offer indirect protection by activating endogenous defence systems and by modulating different physiological processes (Han *et al.,* 2007).

Another group of compounds contained in pollen are the phytosterols. Among several bioactivities the most prominent is their blood cholesterol-lowering effect via partial inhibition of intestinal cholesterol absorption. Other claimed benefits of phytosterols are possible antiatherogenic effects, as well as immune stimulating and antiinflammatory activities carried out mainly by beta-sitosterol. Furthermore, there is emerging evidence suggesting that plant sterols may have particularly beneficial effects against the development of different types of cancers, like colorectal, breast and prostate cancers. It is not clear whether mechanisms other than the established cholesterol-lowering action of phytosterols could also contribute to these potential health benefits (Trautwein & Demonty, 2007).

Antimicrobial activity

After isolation of different flavonoids from *Eucalyptus globulus*, *Ranunculus sardous* and *Ulex europeans* bee pollen it was concluded that the herbacetin derivates from *Ranunculus sardous* and *Ulex Europeans* had a marked antibiotic activity against *Pseudomonas aeruginosa*. On the other hand, *Eucalyptus globulus*, mainly rich in quercetin derivates, did not show any antibacterial activity (Campos, 1997; Campos *et al*., 1998).

In other study it was found that bee pollen hydrophobic compounds with unknown nature had antimicrobial activity against viridans streptococci (Tichy & Novak, 2000).

Antibacterial activity of Turkish bee pollen was studied against 13 different bacterial species pathogenic for plants (*Agrobacterium tumefaciens, A. vitis, Clavibacter michiganensis subsp. michiganensis, Erwinia amylovora, E. carotovora pv. carotovora, Pseudomonas corrugata, P. savastanoi pv. savastanoi, P. syringae pv. phaseolicola, P. syringae pv. syringae, P. syringae pv.*

tomato, Ralstonia solanacearum, Xanthomonas campestris pv. campestris and X. axonopodis pv. vesicatoria). The results showed that the Turkish bee pollen extract had an inhibitory effect against all pathogens. The conclusion of the study indicated that this bee-pollen extract had the potential to became a seed protectant because some of the bacterial pathogens were known to be transmitted via seeds (Basim *et al.,* 2006). However, assays carried out with methanol extracts of Turkish bee pollen at concentrations from 0.02% to 2.5% had no activity against selected spoilage and pathogenic microorganisms (Erkmen & Ozcan, 2008).

Pollen bread was found to possess an antibacterial activity against *Staphylococcus aureus* and *S. epidermidis* (Baltrusaitye *et al.,* 2007a). In a recent study with 80% ethanol extracts of Brazlilian pollen antibacterial activity was exibited against *Staphylococcus aureus, Bacillus subtilis*, *Pseudomonas aeruginosa* and *Klebsiella sp* (Carpes *et al.,* 2007). The antibacterial substances of pollen, active against *Streptococcus viridans* are similar to the ones found in propolis and honey combs (Tichy & Novak, 2000).

Antioxidant and detoxicating activity

An antioxidant is a molecule capable of slowing or preventing the oxidation of other molecules. Oxidation is a chemical reaction that transfers electrons from a substance to an oxidizing agent. Oxidation reactions can produce free radicals, which start chain reactions that damage cells. Antioxidants can be free radical scavengers and participate in this cycle in a way to help in the elimination of the dangerous free radicals and their intermediates, and inhibit other oxidation reactions by being oxidized themselves. As a result, antioxidants are often reducing agents such as thiols or polyphenols.

The radical theory in human physiology claims that active free radicals are involved in almost all of the cellular degradation processes and leads to cell death. Oxidative stress is thought to contribute to the development of chronic and degenerative diseases such as cancer, autoimmune disorders, ageing, cataract, rheumatoid arthritis, cardiovascular and neurodegenerative diseases (Pham-Huy *et al.*, 2008).

In several studies a close relationship between pollen antioxidant bioactivity and phenolic compounds has been reported (Campos *et al.*, 1994 a; Campos *et al.,* 2003; Leja *et al.*, 2007; Le Blanca *et al.,* 2009). However the correlation between these two parameters is not that clear (Marghitas *et al.,* 2009). It was also found that the bee pollen antioxidant activity is species-specific (Almaraz-Abarca *et al.,* 2004; Leja *et al.*, 2007; Le Blanca *et al.,* 2009; Marghitas *et al.,* 2009). and independent of its geographical origin (Almaraz-Abarca *et al.,* 2004). Bee bread was also found to have a high antioxidant activity (Ngai *et al.*, 2004; Baltrusaityte *et al.*, 2007).

The free radical scavenging ability is an interesting property that can be found in other hive products such as propolis (Lima *et al.,* 2009) and bee pollen (Campos *et al.,* 2003). This ability decreases with the storage of dried bee-pollen at room temperature and can loose about 50% of the antioxidant power within 1 year (Campos *et al.,* 2003). Experiments which involved feeding rats with bee pollen were conducted for one month in order to study the state of the erythrocyte redox system. It was established that the content of glutathione, total SH-groups as well as the activities of glutathione peroxidase and glutathione reductase in these animals were increased in comparison with the control group. Simultaneously, a decrease of malondialdehyde and dienic conjugates in erythrocytes was show. The activity of catalase and superoxide dismutase was increased but the effect was not statistically significant. It was concluded that the antioxidative system is non specifically activated and that the oxidative processes in erythrocytes are blocked (Dudov & Starodub, 1994).

Primary and secondary humoral immune response (the level of specific IgM and IgG) together with the intensity of delayed-type hypersensitivity to sheep erythrocytes were investigated in rabbits fed with bee pollen load for a month. It is shown that bee pollen was an immunomodulator. It stimulated humoral immune response and changed the reaction of delayed-type hypersensibility (Dudov *et al.*, 1994).

The effect of bee pollen on intercellular lipofuscin in mice was studied by morphological observations. The results demonstrate a reduction of lipofuscin in cardiac muscle, liver, brain and adrenal glands following administration of bee pollen (Liu & Li, 1990). The effect of bee pollen on liver functions in old rats was studied by Uzbekova *et al.,* (2003). After one month they had a diminution of malondyaldehyde levels and the sulphydryl groups (SH-G) content was normalized. Also serum urea and protein levels were significantly improved at the end of the experiments (Uzbekova *et al.,* 2003).

In traditional Chinese medicine a mixture of bee pollen, radix polygoni multiflore, *Ziziphi spinosae* semen, *Radix salviae multiorhizae*, *Fructus schisandrae* and *Fructus ligustris lucidae*, known as "NaO Li Su", has a reputation as a medicine against declining memory functions. In the present study the effect of this mixture on failing memory was assessed in 100 elderly Danish volunteers by a double-blind placebo controlled cross-over trial. The effect was evaluated after treatment periods of 3 months duration by a battery of psychological and biochemical tests. No desirable effects on memory functions were achieved with this treatment. Increases in the number of red blood cells and in the serum creatinine levels were seen after treatment. In the subgroup initially showing a number of red blood cells below the median a significant positive correlation was found between changes in the number of red blood cells and changes in the Wechsler Memory Scale scores (Iversen *et al.*, 1997).

The free radical scavenging activity prevents irradiation damage by free radicals. This means that an antiradiation effect of pollen should be expected (Pham-Huy *et al.*, 2008). It was established that small x-irradiation doses activated the lipid peroxidation and antioxidant system enzymes in mice liver. The introduction of a bee pollen extract to the diet of the animals normalized the activity of several glutathione system enzymes in mice liver (Bevzo & Grygor'eva, 1997).

Chronic combined exposure to ionizing radiation of 0.25 Gy and cadmium chloride or atrazine in drinking water at five-fold Limited Permissible Concentration (LPC) values led to an additively reduced intercellular K+ level in rat brain, caused by the active ion transport disorders due to irradiation and to changes in membrane permeability, in the case of toxic loading. Application of beta-carotene oil or bee-pollen both abolished radiation effects but did not influence the effects caused by chemical toxics. The authors supposed that the selective action of the observed drugs was connected with the antioxidant activity of pollen and beta-carotene (Ananeva & Dvoretskii, 1990).

Bee pollen extracts were administered to rats, intoxicated by carbaryl. Levels/activities of total protein, albumin, glucose, triglyceride, T-cholesterol, T-bilirubin, blood urea nitrogen, creatinine, uric acid, magnesium, sodium, potassium, chloride as well as different liver enzymes were evaluated in the serum samples of the treated rats in comparison to the controls, showed a detoxication effect of bee pollen. While carbaryl caused negative changes in most of the oxidative stress markers and of the serum biochemical parameters investigated in the controls, these effects were relieved with the administration of bee pollen (Eraslan *et al.,* 2008 a).

It was recently found that feeding mice with bee pollen protects from the toxical effects of the pesticide protoxur, a very toxic pesticide, which is thought to induce oxidative stress (Eraslan *et al.,* 2008 b).

Paracetamol intoxicated rats fed pollen extract preparations, Cernilton and Cerniltin showed that Cernilton increased the survival of the rats by preventing hepatic lesions. It has been hypothesized that this action is effective and not prophylactic (Juzwiak, 1993).

Enzymatic hydrolysates from bee pollen of *Cistus ladaniferus* prepared by six proteases and angiotensin I - converting enzyme (ACE) inhibitory activities were investigated. The activities of these hydrolysates were extremely high, similar to the ones encountered after various fermented foods such as fish sauce, mirin, sake, soy sauce, vinegar, cheese, miso, natto, and so on. These results suggest that there is a very high antioxidant and ACE inhibitory activities in hydrolysates from bee pollen of *Cistus ladaniferus* (Nagai *et al.,* 2007).

Antiinflammatory activity

Inflammation is a physiological response to the damage of tissues or cells that is caused by physical or biological agents, involving different reactions intended to remove the cause and repair the damage.

The antinociceptive and antinflammatory activity of pine (*Pinus densiflora*) flower pollen extracts (100 and 200 mg/kg) in mice were tested. The positive results of pollen on acid acetic- induced writhing, on formalin-induced paw licking and on the hot plate test suggest that the analgesic effect may be related to the antinflammatory, neurogenic and narcotic properties of pollen. Positive results in carragenan-induced paw oedema and arachidonic acid-induced ear oedema suggest that *Pinus densiflora* pollen extract acts on cycloxygenase and lypoxygenase activities (Choi, 2007).

Benign prostatic hyperplasia

The most important use of pollen in medicine is its prophylactic and curative activity in prostate disorders. Prostatitis, or prostate inflammation, can cause difficult or painful urination that is often accompanied by a burning sensation, by a strong and frequent urge to urinate, that often results in only small amounts of urine, and by pain in the lower back or abdomen. Benign prostatic hyperplasia (BPH) is an enlarged prostate, benign meaning non-cancerous and hyperplasia, excessive growth of the tissue. BPH is the result of small non-cancerous growths inside the prostate. Chronic prostatitis is very common in elderly men, which might be related to age and hormone changes. As conventional therapies such as antibiotics are not efficient, it is not surprising that patients have turned with increasing frequency to phytotherapy and other complementary treatments, including the intake of pollen. Indeed, most of the studies reported in this section have been carried out with different flower pollen preparations, as described in the next paragraphs, but there are also some positive results with bee pollen.

Flower pollen preparations

Most clinical tests were conducted with different flower pollen preparations: Cernitron, Cernitol and Prostat/Poltit are preparations of hand collected grass or rye pollen while Cernitin and Graminex contain different flower pollens.

In the Bruneton's Compendium of Pharmacognosy it was mentioned that in certain countries an extract of flower pollen from a selected flora in the South of Sweden was commercialised for prostatitis. The active extracts included two fractions, one was water-soluble and the other was soluble in acetone and rich in sterols. The hydrosoluble fraction from AB Cernelle, (Vegeholm, Sweden), was analysed and inhibited *in vitro* tumour and normal prostatic cells. The total extract decreased the prostate hypertrophy in rats, but given to humans no change was verified in blood levels of LH, FSH, testosterone or dihydro-testosterone. In patients with prostatic adenoma the improvement was in nycturie, important decreases in the residue post-urinate and in long term treatment, also decrease in the diameter antero-posterior of prostate. The urinary debit did not suffer any changes. The effect on the other symptoms usual in the hyperthrophie benign of prostate was not of statistical significance (Bruneton, 1999).

The bioactivity described above is attributed to 2,4-dihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one (DIBOA), a cyclic hydroxamic acid (Zhang *et al.*, 1995). This hydroxamic acid is an active compound in the flower pollen extract Cernitin which might be responsible for the symptomatic relief in patients with benign prostate hyperplasia. Seventy nine patients, ages ranged from 62 to 89 years, with this disease were treated with pollen extract, resulting in a mild beneficial effect on prostate volume and urination (Yasumotor *et al.,* 1995).

The pollen extract Prostat/Poltit (produced by Allergon) shows in a double blind placebo controlled study an improved symptomatic relief in man with chronic nonbacterial prostatitis/ chronic pelvic pain syndrome (CNBP/CPPS). After 6 months the patients treated with Prostat/Poltit (3 tablets/day eq. 222 mg of pollen extract/day) showed a significantly lower pain score, less of voiding symptoms, less urine storage symptoms and better sexual function than the patients who had received placebo. No adverse effects were reported (Elist, 2006).

An overview of one promising pharmacologic agents in complementary medicine for their use in benign prostatic hyperplasia and prostate cancer agents, showed that Cernilton (the cited rye pollen extract) is one of them, besides *Glycine max* (soy), PC-SPES (a mixture of 8 herbs) and *Prunus africana (Pygeum africanum;* Tadenan) (Thompson, 2001) Cernitron was also tested in a study with 15 patients with chronic prostatitis and prostadynia. In 13 of the patients there was either complete or lasting relief, 2 patients failed to respond (Buck *et al.,* 1989). Another double blind study showed a significant improvement of the Cernitron treated patients in comparison to the controls (Buck *et al.,* 1990). Ninety patients were treated with the same product and were divided into two groups, with and without complicating factors. Those without such factors (n = 72) 78% improved significantly. In the other group (n = 18) only 1 patient showed a positive response. Cernitron was well tolerated by 97% of the patients (Rugendorff *et al.*, 1993).

A clinical assay with Cernitron with a total of 89 patients with benign prostatic hyperplasia (BPH) that were treated pharmacologically for 4 months: 51 received Cernilton and 38 received Tadenan (controls). Significant subjective improvement was found in 78% of the patients in the Cernilton group compared to only 55% of the Tadenan-treated patients. In the Cernilton-treated patients a significant improvement in the uroflow rate, decrease in residual urine and in prostate volume were found. This study shows that Cernilton is an effective therapy for patients with BPH (Dutkiewicz, 1996).

Bee pollen

The morphological changes in aged canine prostatic hyperplasia were followed after bee pollen treatment, 5-10 g/kg administered in oral doses for 2 months to aged dogs with prostatic hyperplasia. Prostate size was reduced both at 1 and at 2 months. Microscopic examination showed marked diminution in gland diameter, epithelial cell heights and less papillary infolding of the epithelia compared to untreated controls. No effect on plasma estradiol or testosterone levels was observed and no toxicities were reported (Lin *et al.*, 1990).

A double-blind, placebo-controlled clinical trial was performed to investigate the efficacy and safety of 12-week intake of a bee pollen extract (PE) supplemented food in 47 patients with benign prostatic hyperplasia (BPH). The participants were randomly assigned to 3 study food trial groups: a placebo group (0 mg extract per day); a lower-dose group (160 mg PE per day); and a high-dose group (320 mg PE per day) (Groups P, L, and H, respectively). Outcome measures were the change during the 12-week intervention period in subjective symptom scores and 2 urodynamic parameters, maximum flow rate (Q (max)) and residual urine volume. Q (max) values were significantly increased in Group H ($P < 0.05$) but not in Groups L or P. While residual urine volume was significantly increased in Groups L and P ($P < 0.05$ each), the level in Group H decreased, although the difference between Groups H and P did not reach statistical significance ($P = 0.052$). No pollen-related health hazards or laboratory abnormalities of clinical significance were found. The results can be summarized that a higher dose of bee pollen extract intake significantly decrease the symptoms of BPH (Mupakami *et al.*, 2008).

Biologically active substances

One of the components responsible for antiprostatitic activity is quercetin and this is also one of the main flavonoids in bee pollen (Campos *et al.,* 1997). This compound shows *in vitro* a permanent inhibition of androgen-independents cancer cells PC-3 at a dose of 100 μM. In prostate cancer cells this activity is due to the ability of quercetin to block the cell cycle in various phases through an inhibition of the expression of several specific genes. Quercetin also up-regulates expression of various tumour suppressor genes while down-regulating oncogene expression (Lima *et al.*, 2009).

In a prospective, double blind, placebo-controlled trial, the patients who had been taking quercetin (500mg, 2 time/day for 4 weeks) showed a significant improvement in NIH chronic prostatitis symptoms, 67% of the patients taking quercetin having a significant decrease of symptoms (Shoskes, 2002).

Kaempferol, another bee pollen flavonoid caused a reversible growth inhibition of PC-3 cancer cells (Hari *et al.,* 2004). It is known that other flavonoids present in pollen (e.g. apigenin) are able to depress the kinase activation in prostate cancer (Lepley *et al.*, 2008).

Another class of substances that might be involved in the antiprostatitis action of bee pollen are the phytosterols. Besides cholesterol other sterols in pollen are fucosterol, beta-sitosterol, stigmasterol and campesterol. Like other components the amounts and sterol types vary depending on the plant species (Stanley &

Linskens, 1974). Beta-sitosterol is known to be an active substance against BPH (Klippel *et al.*, 2003).

Anaemia and the hemopoietic system

Anaemia is characterized by a low number of red blood cells. Research related to this disease has been carried out with bee pollen and other bee products. The effects of 10 g/kg/day of oral bee pollen on haemolytic anaemia animals were studied on the hemopoietic system of mice and rats. The results showed that bee pollen markedly antagonised the inhibition of the hemopoietic system and reduced white blood cells in these animals (Wang *et al.*, 1993). Intake of bee pollen by rats induced a significant increase in red blood cells (Chauvin, 1968).

Similar studies in healthy rats and rats with nutritional ferropenic anaemia were carried out, examining the effect of the addition of 10 g/kg/day of multifloral bee pollen on a standard diet. The bee pollen group showed a better weight gain, an increase in the haemoglobin levels and a decrease in platelets. Platelet concentration constitutes a haematic parameter that reflects the state of the iron within an organism. It was deduced that bee pollen improves the digestive absorption of iron (Haro *et al.*, 2000).

In one clinical study with 20 patients that consumed pure bee bread their health was improved showing a better appetite and weigh gain. This was accompanied by increasing haemoglobin and red blood cells (Leonawitschjus, 1976). Quercetin and rutin, both flavonoids found in bee pollen were tested in sickle red blood cells *in vitro*. The results showed a better activity of quercetin as antioxidant. The level of oxyhaemoglobin increased while the levels/ activities of metahaemoglobin, haemichrome, lipid peroxidation and the binding of haemoglobin to the sickle red blood cell membrane decreased (Cesquini *et al.,* 2003).

More clinical studies with humans are necessary to confirm the promising results found in animal studies.

Antiosteoporosis effects

Osteoporosis is defined as a reduction in bone mass and disruption of bone architecture resulting in reduced bone strength and increased fracture risk.

In a recent study Hamamoto *et al.* (2006) show that bee pollen water-solubilized extract from *Cistus ladaniferus* has an inhibitory effect on bone resorption in rats femoral tissues and osteoclastic cell formation in bone marrow cell culture *in vitro*. Thus bee pollen extract has stimulatory effects on bone formation *in vitro* (Hamamoto *et al.,* 2006 b). The active factor of this effect, a bee pollen protein, has been characterised (Hamamoto *et al.,* 2006 a).

It was shown by the same research group that water-solubilized extract from *Cistus ladaniferus* pollen caused a significant increase of alkaline phosphatase, an enzyme that participates in bone mineralization. This increase was completely inhibited in the presence of cycloheximide, an inhibitor of protein synthesis. This suggests that the activity of bee pollen on bone formation can result from newly synthesized protein components. The oral administration of the water-solubilized bee pollen extract from *Cistus ladaniferus* to rats caused a significant increase in calcium content, alkaline phosphatase activity and DNA content in the femoral-diaphyseal and metaphyseal tissues, indicating that the extract exerted anabolic effects on bone components *in vivo*. (Yamaguchi *et al.*, 2006).

The water-solubilized extract from *Cistus ladaniferus* bee pollen has a preventive effect on bone loss in STZ-diabetic rats, and also a restorative effect on serum biochemical factors in diabetic rats (Yamaguchi *et al.*, 2007).

Antiallergenic properties

Airborne pollen is known to cause allergic reactions. However, there are promising results that pollen can also be used to prevent these allergies. Claims that a small consumption of bee pollen can desensitise against hay fever have been known for a long time. However, only recently it was proven that bee pollen indeed exerts antiallergic and anti-hay fever effects.

The antiallergic activity of bee pollen phenolic extract BPPE and the flavonoid myricetin (MYR) was tested in a murine model of ovalbumin (OVA)-induced allergy in mice. BPPE (200 mg/kg) and MYR (5 mg/kg) treatments showed inhibition of different allergic reactions. The results support the hypothesis that MYR is one of the flavonoids of BPPE responsible for the anti-allergic effect and a potential tool to treat allergy (Medeiros *et al.,* 2008).

Since mast cells play a central role in the pathogenesis of various allergic diseases, the effect of bee pollen ingestion significantly reduced the cutaneous mast cell activation elicited specific antigens. It also reduced *in vitro* mast cell degranulation and tumour necrosis factor-X production. These results revealed that the antiallergic action of bee pollen was exerted by inhibiting the activation of mast cells, which plays important roles, not only in the early phase, but also in the late phase of the allergic reaction (Ishikawa *et al.,* 2008).

Grass pollen is a promising agent for the treatment of persons suffering from allergies towards grass pollen allergy (Kahlert *et al.,* 1999; Wachholz *et al.*, 2003), but also following bee stings (Francis *et al.,* 2003; Nouri-Aria *et al.,* 2004). In a clinical test with children allergic to grass pollen, extracts of pollen were administered orally and subcutaneously, the latter treatment was the most efficient (Rebien *et al.,* 1982).

In a recent publication a successful clinical trial in of the sublingually applied *Gramineae* pollen vaccine against hay fever of humans has been reported (Moingeon *et al.*, 2008). A successful therapy with a pollen based vaccine against birch delivered sublingually and subcutaneously has also been reported (Khinchi *et al.,* 2002). These results are very promising due increasing incidence of hay fever in developed countries.

Aqueous pollen extract has been successfully used against house-dust asthma (Wortmann, 1977). A preparation from different bee pollen, called Pollysat was also used for decreasing the symptoms of hay fever (Rimpler, 2003).

Other miscellaneous therapeutic effects

Bee pollen

Cardus bee pollen was shown to have a hepatoprotecting effect in mice (Cristea *et al.,* 1976). These positive effects were confirmed in humans. Administration of pollen bread to patients suffering from chronic hepatitis showed that after 30 days their clinical situation improved measured by the albumin/globulin proportion in plasma and the microscopic structure of liver (Ialomiteanu *et al.,* 1976). These effects could be explained by the pollen induced activation of the antioxidant system liver enzymes and the decrease of lipid peroxidation (Bevzo & Grygor'eva, 1997)

Bee pollen was ingested by 10 patients suffering from hypertriglyceridemia which were under permanent kidney dialysis. After 2 weeks the level of serum triglyceride dropped and after 2 months it reached normal values. The authors conclude that the positive pollen effect can be used for the treatment of hypertriglyceridemia and possibly also of uricaemia (Koslik & Takac, 1979).

A 40 g dose of bee pollen was administered daily to patients after heart failure. The cholesterol blood level diminished significantly, together with lowering of blood viscosity, and sinking concentrations of fibrin and fibrinogen (Liusov *et al*., 1992).

Bee pollen extracts from *Eucaliptus globulus* labill. and *Salix atrocinerea* Brot were tested on Swiss OFFI mice. The results showed that both bee pollen species have antidiarrhoeal activity. However, they have some differences, *Eucaliptus globulus* Labill. bee pollen extract was more effective on retarding the diarrhoea, whereas *Salix atrocinerea* Brot. had a better effect in reducing the percentage of diarrhoeal excrements. Both floral types reduced the diarrhoeal excrements by 30%. This study concluded that the antidiarrhoeal activity, of the studied bee-pollen, may be due to polyphenolic compounds, especially quercetin, although some others compounds could have a role on this activity and may be responsible for the differences on the results (Campos, 1997).

Ludyanski (1994) summarises the long experience with therapeutical use of bee pollen in a large Russian hospital. Treatment with 30-40 g bee pollen daily has had following success rates in percentage of the total persons involved in the treatment of the following diseases: gastritis, 90% (52); anaemia 72% (36); posttraumatic asthenia syndrome, 84% (96); impotency, 68% (65); geriatric conditions 100% (23). The number of brackets indicates the number of patients in each of the treatments (Ludyanski 1994).

In the bee product monograph of Shkederov and Ivanov, good success rates with bee pollen in humans of Eastern Europe have been reported for following diseases: duodenal and gastric ulcer, hypochromic anemia and chronic gastritis (Shkederov and Ivanov, 1983).

Flower pollen

Therapy-relevant research has been carried mainly with different flower pollen preparations: Cernitol, Cernitron and Cernitin.

Cernitin has different beneficial properties: lowering serum lipid levels (Samochowiec & Wojcicki, 1981; Wojcicki & Samochowiec, 1984), reducing atherosclerosis plaque intensity (Wojcicki *et al.,* 1986) and decreasing platelet aggregation both *in vitro* (Kosmider *et al.,* 1983) and *in vivo* (Wojcicki & Samochowiec, 1984). These assays have been confirmed in humans (Wojcicki *et al.,* 1983). Studies in humans suggest that a diet supplemented with polyunsaturated fatty acids decreases whole blood viscosity and reduces triglyceride and cholesterol levels in patients with cardiovascular disease. Having in mind all the above mentioned studies the fatty acid composition of the fat-soluble pollen extract Cernitin GBX was analysed by gas chromatography with regard to its proven antiatherosclerotic activity (Seppinen *et al.,* 1989) The analyses of the fat-soluble pollen extract revealed that the major part (more than 60%) of the fatty acids was in the free form. Linolenic acid (omega-3, 18:3 n-3, a-ALA) an essential fatty acid is the main component with about 70%. If fatty acids are involved in the referred beneficial effects, the role of alpha-linolenic acid as a precursor of eicosapentaenoic acid (omega-3, 20:5 n-3, EPA) is significant, since EPA is considered to be responsible for reduced platelet aggregation. Cernitin intake influenced positively the activity of urinary bladder of rats and mice (Nakase *et al.,* 1990; Nagashima *et al*., 1998).

Pollen extracts are reported to produce good results in patients suffering from nutritional problems in the form of emaciation, loss of appetite and physical and mental asthenia. These effects have been noted both in children and elderly patients convalescing after various illnesses. In particular, protein synthesis increased as did secretion of 17-OH-steroids and 17-oxi-steroids. No side effects being attributed to the Cernitrin intake were shown as being attributed to the preparation, and significant results were achieved after as little as two months of treatment (Dubrisay, 1972; Leparq, 1973).

Side effects and allergic reactions

Bee-pollen is normally well tolerated, but the presence of allergenic pollens and substances can not be excluded. Pollen allergy like hay-fever, concerns mainly allergy against airborne pollen, while allergies to ingested pollen are relatively rare, with a similar rate as other foods. The allergenic effects of bee pollen have been reviewed (Traidl-Hoffmann *et al.,* 2003).

Allergy after ingestion of pollen of the composite family was reported (Cohen *et al.,* 1979) A case of a 34-year-old Spanish woman with a lifelong history of seasonal rhinoconjunctivitis and honey intolerance which developed eosinophilic gastroenteritis after ingestion of bee pollen (Puente *et al.,* 1997). Non-life-threatening anaphylactic reaction has been recorded after bee pollen intake (Geyman, 1994; Greenberger & Flais, 2001). It is recommended that people who are susceptible to allergies or asthma should avoid bee pollen.

Conclusions

This review shows that bee pollen has realistic potential for use in nutrition and therapy. The main bioactivities for medical practice in developed countries seem to be in the decrease of the symptoms of prostatitis and in desensitization against hay fever. However, the treatments of these diseases were carried out with specific flower pollen preparations rather than bee pollen. Most other therapeutic effects published in scientific journals were achieved by extracts from bee pollen and with flower pollen preparations and there are fewer references with whole bee pollen despite is certainly more widely used also against other diseases in developing countries and in traditional medicine. The prescribed quantities for the intake of whole pollen are relatively high, about 30 to 40 g per day(Ludyanski, 1994; Rimpler, 2003).

Summarizing the evidence, it is clear that there is quite a long road until bee pollen will be accepted in modern phytomedicine. The main difficulty for the use of bee pollen in therapy lies in the wide variation of its composition, and thus of its biological activity, depending on its botanical origin. In the first place beekeepers should offer a good selection of different specific bee pollen. Indeed, the harvest of monofloral pollen is possible, but for the time being it is a relatively rare specialty. Another possibility of having a more standardized bee pollen is to mix different pollen types for obtaining a constant composition, and thus also of the biological activity. For this purpose biological parameters like antioxidant activity and vitamin content should be included in a future bee pollen standard. Monofloral or standardized bee pollen should be tested in future biological and clinical studies. The biological and pharmacological properties of the monofloral pollen types should be determined and the biologically active substances identified. In a final step pollen types with optimal pharmacological properties can be tested in human therapy.

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